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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/381,032	12/17/1999	ANDREAS BERGMANN	PM263260	3417

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/381,032	Applicant(s) BERGMANN ET AL.	
	Examiner Phuong Huynh	Art Unit 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 April 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *25 April 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *None*.
   Claim(s) rejected: *23-25, and 27-33*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Claims 23-25, and 27-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vitti *et al* (of record, Acta Med Austriaca 23(1-2): 52-6, 1996; PTO 892) in view of Harlow et al (of record, in Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory 1988, pages 556, 564-591), and Nicholson *et al* (of record, J Mol Endocrinol 16(2): 159-70, 1996; PTO 892) or Morgenthaler *et al* (of record, J Clin Endocrinol Metab 81(2):700-6, Feb 1996, PTO 892).

Applicant's amendment filed 4/25/05 have been fully considered but not found convicing for the same reasons set forth in Office Action mailed 1/24/05. Applicants submit that there is no sufficient suggestion to combine the references in the 103(a) rejection in the manner proposed by the Examiner or there is no reasonable expectation of successfully combining them to obtain the present invention. Vitti et al discuss a new in vitro bioassay for TSH antoantibodies that measures cAMP production in Chinese hamster cells transfected with human TSH receptor. This assay does not discuss a competition with any labeled TSH (as in the present invention) and even suggests that improved sensitivity with respect to the TRAK assay may be obtained with this technique. In addition, although Vitti et al mentions the TRAK assay, this technique is a liquid phase technique which requires precipitation. Contrary to the Examiner's remarks, no porcine TSH receptor is ever immobilized to a plate in the TRAK assay. As eidence of the superior and unexpected nature of the presently claimed invention, the Applicants draw the Examiner's attention to Costagiola et al which provides a comparison of the conventional radioreceptor assay (e.g., the TRAK assay) and those of the present invention (e.g., the TRAKhuman assays). As can be seen from the abstract, "a specificity of 99.6% with a sensitivity of 98.8% was obtained for the solid state assays, while a "specificity of 99.6% and 80.2% sensitivity" was obtained for the solution phase assay. Although these references cited in the rejection could, conceivably, suggest the use of antibodies for detecting TSH receptor autoantibodies in Graves' disease, they hardly suggest the use of autoantibodies to immobilize a functional human TSH receptor preparation in order to design an improved solid phase competitative assay. Furthermore, Nicholson discusses both A10 and A11 antibodies binding to the same short peptide seuqence comprising amino acids 22-35 of human TSH receptor. Borth monoclonal antibodies A10 and A11 are therefore sequential antibodies, obtained by immunization with an antigen, in which said amino acids apparently are eposed and can act as an antigen. By treatment with acetone, the native receptor is denatured and siad sequence become accessible.

In response to applicants' argument that there is no suggestion to combine the reference, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In this case, the teachings of Vitti reference pertaining to the use of recombinant human TSH receptor expresed in CHO cells as well as the use of radiolaled bovine TSH to porcine TSH receptor in conventional TRAK assay, the teachings of Harlow et al indicating the advantage of using receptor specific antibody to immobilized receptor to a soblid support for detection of any autoantibody, and the teachings of Nicholson and Morganthaler indicating the success of using recombinant human TSH receptor antibodies for detecting TSH

receptor autoantibodies in Graves' disease would have led one of ordinary skill in the art at the time the invention was made to combine the references to use recombinant human TSH receptor to detect human specific TSH receptor autoantibodies. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In response to applicants' argument that Vitti does not discuss any labeled TSH as in the present invention, Vitti et al teach autoantibodies to TSH receptor are measured in most laboratories by their ability to inhibit the binding of radiolabled TSH to its receptor (see page 53, col. 1, Introduction, second paragraph, in particular) and that conventional TSH receptor autoantiboodies are measured using conventional TRAK assay that uses radioreceptor asay based on inhibition of binding of 125 idodine bovine TSH to porcine TSH receptor (see page 53, col. 2, TSH-Receptor Antibodies, in particular).

In response to applicants' argument that no porcine TSH receptor is ever immuobilized to a plate in the TRAK assay and TRAK assay, Harlow et al teach immobilized receptor to a solid support such as a tube using receptor specific antibody and the advantage of the assay is that it is rapid, easy, quantitative and sensitive (see page 584, in particular).

In response to applicants' argument that Costagiola et al provides unexpected results of the present claimed invention, the results would have been expected (rather than unexpected) to one of ordinary skill in the art at the time the invention was made because the use of recombinant human TSH receptor to detect human TSH autoantibodies instead of porcine TSH receptor to detect human autoantiodies in the conventional TRAK assay would improve the specificity of the assay as claimed.

In response to applicants' argument that the antibodies such as A10 and A11 are sequential antibodies instead of monoclonal antibody that recognizes only conformational epitopes of the human TSH receptor, Nicholson also teach monoclonal antibody such as A9 that recognizes conformational epitopes of the human TSH receptor (see page 167, col. 1, last full paragraph, in particular). In fact, the instant specification discloses "it should be emphasised that, although conformational antibodies are very particularly suitable for immonbilizing rhTSHR, the remaining anti-hTSHR-mab 1-8 also functional" (see page 31, last paragraph, in particular).

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